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Synthesis of 2-(1H-imidazo[4,5-b]pyridin-2-ylimino)-5-arylidenethiazolidin-4-ones,1-(1H-imidazo[4,5-b]pyridin-2-yl)-5-methyl-3-aryl-1,3,5-triazinane-2-thiones and 3-(1H-imidazo[4,5-b]pyridin-2-yl)-5-aryl-1,3,5-oxadiazinane-4-thiones

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ABSTRACT

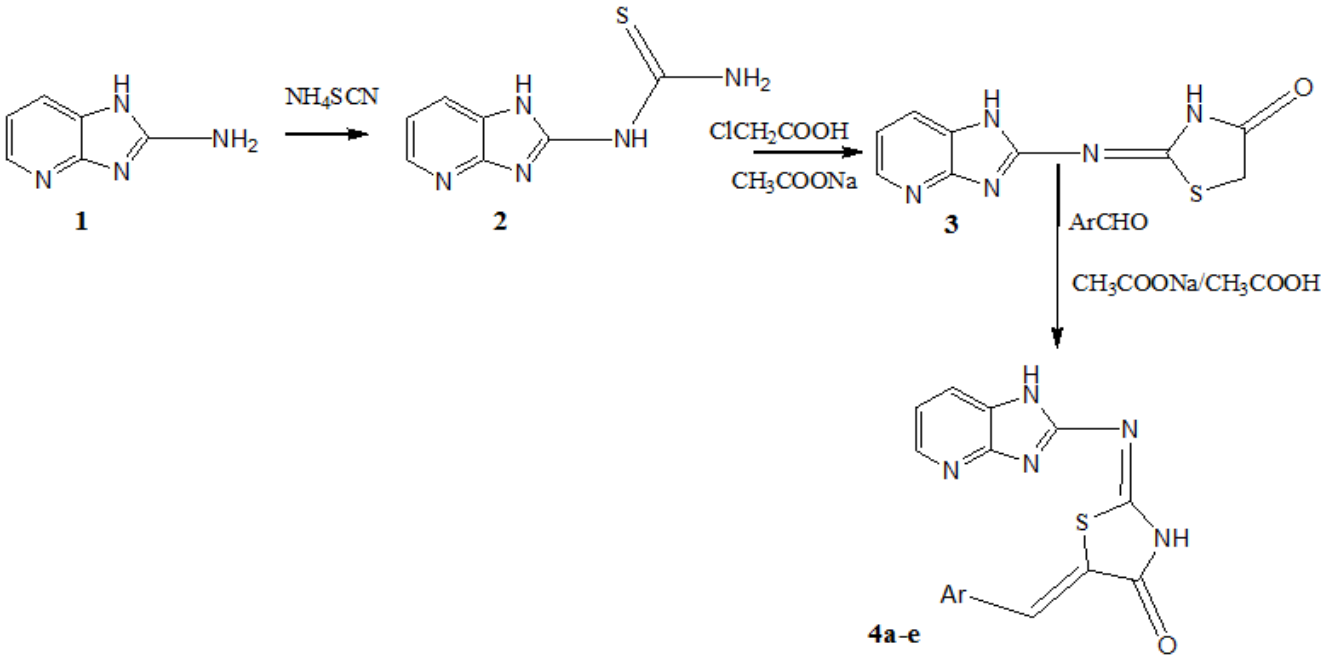
1H-imidazo[4,5-b]pyridin-2-amine **(1)** reacts with ammoniumthiocyanide to form 1-(1H-imidazo[4,5-b]pyridin-2-yl)thiourea **(2)**, which on reaction with chloroacetic acid gives 2-(1H-imidazo[4,5-b]pyridin-2-ylimino)thiazolidin-4-one **(3)**. Compound **3** on condensation gives 2-(1H-imidazo[4,5-b]pyridin-2-ylimino)-5-arylidenethiazolidin-4-ones **(4a-e)**. Further 1H-imidazo[4,5-b]pyridin-2-amine **(1)** reacts with aromatic isothiocyanates to form compound **5** which is cyclized to 1-(1H-imidazo[4,5-b]pyridin-2-yl)-5-methyl-3-aryl-1,3,5-triazinane-2-thiones **(6a-e)** and 3-(1H-imidazo[4,5-b]pyridin-2-yl)-5-aryl-1,3,5-oxadiazinane-4-thiones **(7a-e)**.

Key words: Synthesis; Thiones; Heterocycles

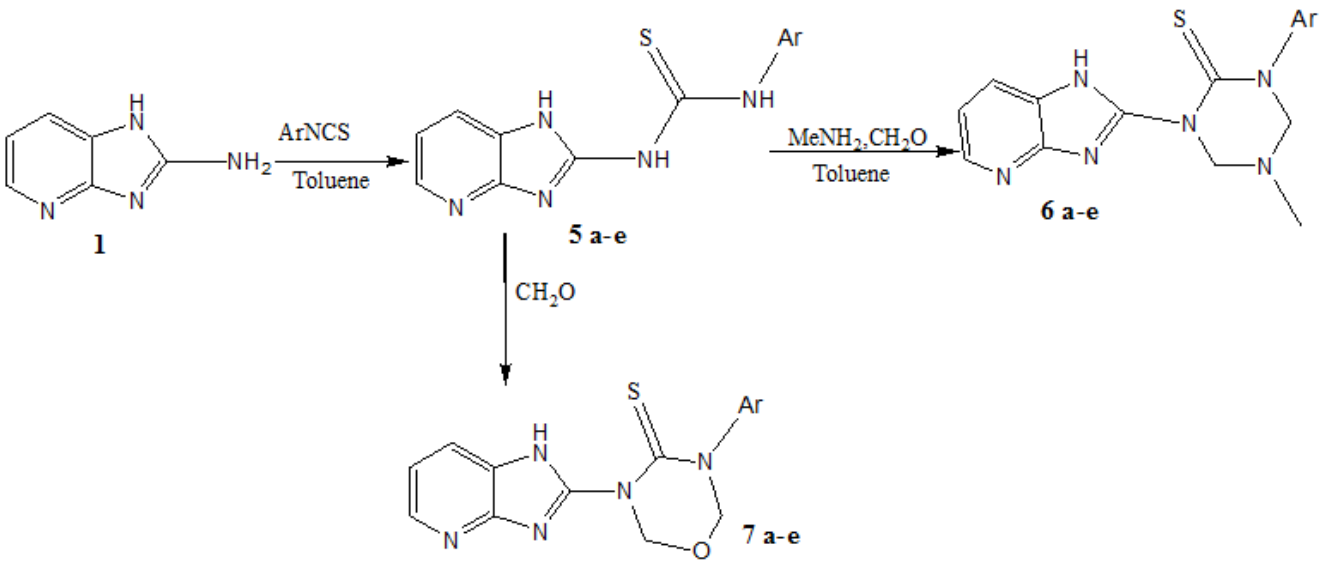
1. INTRODUCTION

Small ring heterocycles containing nitrogen, sulfur and oxygen have been under investigation for a long time because of their important medicinal properties. Among these types of molecules, 4-thiazolidinones have been shown to have various important biological activities such as antibacterial, antifungal, antiviral, diuretic, antituberculostatic, anti-HIV, antihistaminic, anticancer, anticonvulsant, antiinflammatory and analgesic properties (Capan et al. 1999; Vigorita et al. 2001; Kavitha et al. 2006; Ottana et al. 2005; Kucukguzel et al. 2006; Asif, 2020; Malik et al. 2020). 1,3,5-triazinan-2-ones are

useful for the protection of amino groups, as well as for the synthesis of polyamines, poly functional aminoalcohals and water soluble triazinan-2-onesare used as fertilizers. Very few reports are available on the synthesis of heterocyclic 1,3,5-triazinan-2-ones (Knapp et al. 1992; Jasys et al. 1988; Hawkim,1988; Hardies, 1979a; Hardies, 1979b; Rajanarendar et al. 2004; Pradipet al. 2005; Rajanarendar 2005; Haedy, 2011; L axminarayana et al. 2008), and 1,3,5-oxadiazinan-4-ones.



Scheme 1



Phenyl, 4-Chlorophenyl, 2-Chlorophenyl, 4-Fluorophenyl, 4-Bromophenyl

Scheme 2

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2. EXPERIMENTAL SECTION

Chemicals and solvents were reagent grade and used without further purification. Melting points were determined on a capillary melting point apparatus and are uncorrected. The ^{1}H NMR was recorded in the indicated solvent on a Varian 500 MHz spectrometer with TMS as internal standard. All chemical shifts (δ) were reported in ppm from internal TMS. Mass spectra were measured on a Jeol JMS D-300 spectrometer. Infrared spectra were recorded in KBr on Brucher-IFS-66 FTIR spectrophotometer. The homogeneity of the compounds was checked using precoated TLC plates (E.Merk Kieselgel 60 F_{254}).

1-(1H-imidazo[4,5-b]pyridin-2-yl)thiourea (2)

Equimolar amine **(1)** (0.02mol), and ammonium thiocyanate (1.5g, 0.02mol) were dissolved in ethanol containing 2ml of Conc. Hydrochloric acid. The reaction mixture was refluxed for 1hr. Then, it was cooled in ice-water mixture. The precipitate obtained, strained well, filtered washed with cold water and dried. The crude product was recrystallised from rectified spirit

IR: 3283 cm^{-1}(N-H), 3065 cm^{-1}(C-H aromatic), 1616 cm^{-1}(C=N), 1150 cm^{-1}(C=S),

^{1}H NMR (DMSO-d_6) : δ=7.92- 8.35 (m, 3H), 9.65 (brs, 2H), 12.22 (brs, 1H), 13.11 (brs, 1H).

Mass: m/z 193 (M+H).

2-(1H-imidazo[4,5-b]pyridin-2-ylimino)thiazolidin-4-one (3)

1-(1H-imidazo[4,5-b]pyridin-2-yl)thiourea **(2)** (0.03mol), chloroacetic acid (0.036mmol) and the sodium acetate were dissolved in EtOH and refluxed for 5-6 hrs. After, cooling down to room temperature; the mixture was extracted with CH_2Cl_2. After elimination of the solvent under vacuum, the residue was purified by recrystallisation from EtOH.

IR: 3326 cm^{-1}(N-H), 3033 cm^{-1}(C-H aromatic), 1684 cm^{-1}(C=O), 1536 cm^{-1}(C=N).

^{1}H NMR (DMSO-d_6) : δ= 2.52 (dd, 2H), 7.22 (t, 1H), 7.78 (dd, 1H), (8.23 dd, 1H) 11.81 (brs, 1H) 13.22 (brs , 1H).

Mass: m/z 233 (M+H).

2-(1H-imidazo[4,5-b]pyridin-2-ylimino)-5-arylidenethiazolidin-4-ones (4a-e)

To a solution of 2-(1H-imidazo[4,5-b]pyridin-2-ylimino)thiazolidin-4-one **(3)** (0.01 mole) in ethanol (60 ml), aldehyde (0.01 mole) and CH_3COONa/ CH_3COOH were added and the mixture was refluxed for 10 hours. It was then cooled, concentrated and poured into crushed ice and filtered. The solid thus obtained was purified by recrystallization from ethanol.

2-(1H-imidazo[4,5-b]pyridin-2-ylimino)-5-benzylidenethiazolidin-4-one (4a)

IR: 3429 cm^{-1}(N-H), 3075 cm^{-1}(C-H aromatic), 1761 cm^{-1}(C=O), 1518 cm^{-1}(C=N).

^{1}H NMR (DMSO-d_6) : δ= 6.82 (dd, 1H), 7.22 (dd, 2H), 7.42 (dd, 1H), 7.61 (dd, 2H), 7.93 (d, 1H), 8.11 (brs, 1H), 8.25 (d, 1H), 13.05 (brs, 1H).

Mass: m/z 321 (M+H).

2-(1H-imidazo[4,5-b]pyridin-2-ylimino)-5-(4-methoxybenzylidene)thiazolidin-4-one (4b)

^{1}H NMR (DMSO-d_6) : δ= 2.12 (s, 3H), 6.79 (dd, 1H), 7.21 (dd, 41H), 7.45 (dd, 1H), 7.59 (dd, 2H), 7.91 (d, 1H), 8.10 (brs, 1H), 8.24 (d, 1H), 13.06 (brs, 1H).

Mass: m/z 351 (M+H).

2-(1H-imidazo[4,5-b]pyridin-2-ylimino)-5-(2-methoxybenzylidene)thiazolidin-4-one(4c)

^{1}H NMR (DMSO-d_6) : δ= 2.10 (s, 3H), 6.77 (dd, 1H), 7.22 (dd, 41H), 7.46 (dd, 1H), 7.61 (dd, 2H), 7.89 (d, 1H), 8.11 (brs, 1H), 8.27 (d, 1H), 13.08 (brs, 1H).

Mass: m/z 351 (M+H).

2-(1H-imidazo[4,5-b]pyridin-2-ylimino)-5-(4-cholorobenzylidene)thiazolidin-4-one (4d)

^{1}H NMR (DMSO-d_6) : δ= 6.75 (dd, 1H), 7.22 (dd, 41H), 7.47 (dd, 1H), 7.63 (dd, 2H), 7.89 (d, 1H), 8.11 (brs, 1H), 8.27 (d, 1H), 13.08 (brs, 1H).

Mass: m/z 355 (M+H).

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2-(1H-imidazo[4,5-b]pyridin-2-ylimino)-5-(2-cholorobenzylidene)thiazolidin-4-one(4e)

^{1}H NMR (DMSO-d_6) : δ= 6.69 (dd, 1H), 7.21 (dd, 41H), 7.45 (dd, 1H), 7.63 (dd, 2H), 7.89 (d, 1H), 8.10 (brs, 1H), 8.27 (d, 1H), 13.05 (brs, 1H).

Mass: m/z 355 (M+H).

1-(1H-imidazo[4,5-b]pyridin-2-yl)-3-arylthioureas (5a-e)

To a solution of 1-(1H-imidazo[4,5-b]pyridin-2-yl)thiourea **(2)** (0.01 mole), in dry DMF (20mL) arylisothiocyanate (0.01 mole) was added and the contents were refluxed for 4 hrs. The reaction was monitored on TLC. After the completion of reaction the content was cooled and the separated product was filtered and crystallized from EtOH.

1-(1H-imidazo[4,5-b]pyridin-2-yl)-3-phenylthiourea (5a)

IR: 3328 cm^{-1}(N-H), 3036 cm^{-1}(C-H aromatic), 1752 cm^{-1}(C=O), 1560 cm^{-1}(C=N).

^{1}H NMR (DMSO-d_6) : δ= 6.82 (t, 1H), 7.22 (t, 3H), 7.42 (d, 1H), 7.65 (d, 1H), 793 (d, 1H), 12.22 (brs, 1H), 12.51 (brs, 1H), 13.04 (brs, 1H).

Mass: m/z 269 (M+H).

1-(1H-imidazo[4,5-b]pyridin-2-yl)-3-(4-chlorophenyl)thiourea (5b)

^{1}H NMR (DMSO-d_6) : δ= 6.82 (t, 1H), 7.22 (t, 3H), 7.42 (d, 1H), 7.65 (d, 1H), 7.93 (d, 1H), 12.22 (brs, 1H), 12.51 (brs, 1H), 13.04 (brs, 1H).

Mass: m/z 303 (M+H).

1-(1H-imidazo[4,5-b]pyridin-2-yl)-3-(2-chlorophenyl)thiourea (5c)

^{1}H NMR (DMSO-d_6) : δ= 6.83 (t, 1H), 7.23 (t, 3H), 7.43 (d, 1H), 7.67 (d, 1H), 7.94 (d, 1H), 12.21 (brs, 1H), 12.50 (brs, 1H), 13.04 (brs, 1H).

Mass: m/z 303 (M+H).

1-(1H-imidazo[4,5-b]pyridin-2-yl)-3-(4-fluorophenyl)thiourea (5d)

^{1}H NMR (DMSO-d_6) : δ= 6.82 (t, 1H), 7.22 (t, 3H), 7.45 (d, 1H), 7.65 (d, 1H), 7.93 (d, 1H), 12.20 (brs, 1H), 12.52 (brs, 1H), 13.06 (brs, 1H).

Mass: m/z 287 (M+H).

1-(1H-imidazo[4,5-b]pyridin-2-yl)-3-(4-bromophenyl)thiourea (5e)

^{1}H NMR (DMSO-d_6) : δ= 6.81 (t, 1H), 7.23 (t, 3H), 7.45 (d, 1H), 7.66 (d, 1H), 7.91 (d, 1H), 12.20 (brs, 1H), 12.51 (brs, 1H), 13.04 (brs, 1H).

Mass: m/z 348 (M+H).

1-(1H-imidazo[4,5-b]pyridin-2-yl)-5-methyl-3-aryl-1,3,5-triazinane-2-thiones (6a-e)

A mixture of 1-(1H-imidazo[4,5-b]pyridin-2-yl)-3-phenylthiourea **(5a)** (0.05 mole), formaldehyde (0.1 mmoles) and methyl amine (0.05 moles) was taken in ethanol (20 mL) and refluxed for 4-6 hrs. The reaction was monitored on TLC. After the completion of reaction it was cooled and the separated product was filtered. The crude material was passed through silica gel column and the product was eluted from 60 % ethylacetate and hexane.

1-(1H-imidazo[4,5-b]pyridin-2-yl)-5-methyl-3-phenyl-1,3,5-triazinane-2-thione (6a)

^{1}H NMR (DMSO-d_6) : δ= : 2.25 (s, 4H), 6.52 (d, 2H), 6.81 (t, 1H), 7.45 (t, 3H), 7.85 (d, 1H), 8.41 (d, 1H), 13.01 (brs, 1 H)

Mass: m/z 324 (M+H).

1-(1H-imidazo[4,5-b]pyridin-2-yl)-3-(4-chlorophenyl)-5-methyl-1,3,5-triazinane-2-thione (6b)

^{1}H NMR (DMSO-d_6) : δ= : 2.24 (s, 4H), 6.51 (d, 2H), 6.80 (t, 1H), 7.46 (t, 3H), 7.89 (d, 1H), 8.40 (d, 1H), 13.03 (brs, 1 H)

Mass: m/z 359 (M+H).

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1-(1H-imidazo[4,5-b]pyridin-2-yl)-3-(2-chlorophenyl)-5-methyl-1,3,5-triazinane-2-thione (6c)

^{1}H NMR (DMSO-d_6) : δ= : 2.24 (s, 4H), 6.51 (d, 2H), 6.80 (t, 1H), 7.45 (t, 3H), 7.86 (d, 1H), 8.41 (d, 1H), 13.04 (brs, 1 H)

Mass: m/z 359 (M+H).

1-(1H-imidazo[4,5-b]pyridin-2-yl)-3-(4-fluorophenyl)-5-methyl-1,3,5-triazinane-2-thione (6d)

^{1}H NMR (DMSO-d_6) : δ= : 2.27 (s, 4H), 6.54 (d, 2H), 6.81 (t, 1H), 7.45 (t, 3H), 7.85 (d, 1H), 8.43 (d, 1H), 13.01 (brs, 1 H)

Mass: m/z 342 (M+H).

1-(1H-imidazo[4,5-b]pyridin-2-yl)-3-(4-bromophenyl)-5-methyl-1,3,5-triazinane-2-thione (6d)

^{1}H NMR (DMSO-d_6) : δ= : 2.23 (s, 4H), 6.51 (d, 2H), 6.85 (t, 1H), 7.44 (t, 3H), 7.86 (d, 1H), 8.41 (d, 1H), 13.01 (brs, 1 H)

Mass: m/z 403 (M+H).

3-(1H-imidazo[4,5-b]pyridin-2-yl)-5-aryl-1,3,5-oxadiazinane-4-thiones (7a-e)

1-(1H-benzo[d]imidazol-2-yl)-3-phenylthiourea **(5)** (0.05 mole), was added with 30 % formaldehyde solution (0.1 moles) and the mixture was treated with conc. HCl (5 mL). After heating at 90-95^{O}C for 4 hrs, the reaction mixture was cooled and neutralized with NaOH. The precipitate formed was filtered and passed through silica gel column and the product was eluted from 60 % ethylacetate and hexane.

3-(1H-imidazo[4,5-b]pyridin-2-yl)-5-phenyl-1,3,5-oxadiazinane-4-thione (7 a)

^{1}H NMR (DMSO-d_6) : δ= : 5.35 (s, 1H), 6.41 (d, 1H), 6.71 (t, 2H), 7.23 (t, 3H), 7.75 (d, 1H), 8.45 (d, 1H), 12.85 (brs , 1 H)

Mass: m/z 324 (M+H).

3-(1H-imidazo[4,5-b]pyridin-2-yl)-5-(4-chlorophenyl)-1,3,5-oxadiazinane-4-thione (7 b)

^{1}H NMR (DMSO-d_6) : δ= : 5.34 (s, 1H), 6.40 (d, 1H), 6.70 (t, 2H), 7.22 (t, 3H), 7.76 (d, 1H), 8.46 (d, 1H), 12.86 (brs , 1 H)

Mass: m/z 324 (M+H).

3-(1H-imidazo[4,5-b]pyridin-2-yl)-5-(2-chlorophenyl)-1,3,5-oxadiazinane-4-thione (7 c)

^{1}H NMR (DMSO-d_6) : δ= : 5.35 (s, 1H), 6.41 (d, 1H), 6.71 (t, 2H), 7.23 (t, 3H), 7.77 (d, 1H), 8.45 (d, 1H), 12.87 (brs , 1 H)

Mass: m/z 324 (M+H).

3-(1H-imidazo[4,5-b]pyridin-2-yl)-5-(4-fluorophenyl)-1,3,5-oxadiazinane-4-thione (7 d)

^{1}H NMR (DMSO-d_6) : δ= : 5.34 (s, 1H), 6.40 (d, 1H), 6.73 (t, 2H), 7.22 (t, 3H), 7.78 (d, 1H), 8.44 (d, 1H), 12.88 (brs , 1 H)

Mass: m/z 329 (M+H).

3-(1H-imidazo[4,5-b]pyridin-2-yl)-5-(4-bromophenyl)-1,3,5-oxadiazinane-4-thione (7 e)

^{1}H NMR (DMSO-d_6) : δ= : 5.34 (s, 1H), 6.40 (d, 1H), 6.71 (t, 2H), 7.22 (t, 3H), 7.79 (d, 1H), 8.45 (d, 1H), 12.86 (brs , 1 H)

Mass: m/z 390 (M+H).

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Ethical approval

Not applicable.

Conflict of Interest:

The authors declare that there are no conflicts of interests.

Data and materials availability:

All data associated with this study are present in the paper.

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